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Identifying possible surrogate markers of COVID19 as a supplement to diagnostic testing in Upstate New York

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Title: Identifying possible surrogate markers of COVID19 as a supplement to diagnostic testing in Upstate New York

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Abstract:

Introduction: COVID19 has raised concerns for resource allocation across various sectors of healthcare. At the frontlines, emergency departments are required to triage a wide range of acuity and non-specific symptomology.

Methods: This retrospective study aimed to pave the way for more concrete detection and triage of patients by analyzing symptomology, physical findings, diagnostic testing and relevant hospital course of the 458 suspected cases that initially presented to an academic level one trauma center emergency department between March and August 2020. A total of 202 COVID positive cases were analyzed.

Results: The most common symptoms were cough (70.63%), fatigue (77%), and shortness of breath (59%). There was a significantly higher percentage of abnormal chest imaging in inpatient groups compared to the ED discharge group (42.86% vs 7.0%, $p < 0.01$). Laboratory studies, especially markers of inflammation (CRP, ESR), markers of tissue damage (lactic acid, troponin), and markers of infection were markedly higher and above normal reference ranges in complicated cases ($p < 0.01$). While there is limited data on the sensitivity and specificity of the current nasopharyngeal PCR test, there was no permutation of symptoms, physical findings, diagnostic testing that was more sensitive than that of the current PCR test calculated at 61.1% in our cohort.

Conclusion: Laboratory studies that otherwise are more commonly conducted inpatient, including markers of inflammation, tissue damage, and infection, may be useful in disposition planning of ED patients in conjunction with clinical correlation of presentation and chest imaging.

1. Introduction:

It is evident that coronaviruses have quickly risen to prominence since the turn of the century. The high transmissibility of SARS-CoV-2 has made it not only a major public health threat, but also a burden on

healthcare infrastructure worldwide. COVID19 has raised concerns for resource allocation across various sectors of healthcare and industries. With its rapid spread and advent of novel strains, there is a concern for efficient triage and disposition of patients given the highly variable presentation of disease severity.

At the front lines of the pandemic are emergency departments, where many people with possible COVID19 first present for healthcare. The CDC and WHO quickly established information regarding typical symptomology and screening guidelines. However, established literature remains scarce with most data coming from the initial epicenter in Wuhan, China. The clinical presentation of COVID19 consists of mostly non-specific viral-like symptoms. Most groups have established that cases can present with a wide range of symptomology and it is unclear if any permutation of symptoms could be a reliable indicator of disease or even disease severity. A retrospective study of over 1,000 cases in Wuhan conducted between December 2019 and January 2020 revealed that the most common symptoms are fever and cough at 44% and 67% at the time of diagnosis [1]. Loss of smell and taste is another possible presenting symptom that has gained significant media attention. Based on established literature, the frequency of these symptoms may vary between 2% to 68% [2,3]. Furthermore, there is still a significant number of patients who are either asymptomatic or present atypically who might otherwise fall through the cracks of current screening models. Consequently, effective screening models and improved detection of cases along with potential correlators of disease severity may prove to be paramount in triaging cases that present to the hospital setting.

Hospitals within our communities serve a unique patient population to which current data may not be as applicable. Screening tests are readily available but there is limited data regarding its reliability. Commonly used methods include PCR and various immunoassays testing for antibodies [4]. The sensitivity of the PCR test is limited with estimates around 70% [5]. Another group compared the sensitivity of the PCR test to that of chest imaging (via CT) and found the sensitivities to be 59% and 88% respectively in their particular cohort [6]. Antibody testing can yield results more rapidly, even within

minutes. However, a positive result suggests the possibility of both a current or previous infection [4]. Sensitivity and specificity data of these tests are still developing. As the current situation develops with economic pressure to re-open public venues, efforts to improve detection as a whole and more specifically, linking possible surrogate markers of severe outcomes becomes even more important, particularly amongst those who are asymptomatic or present atypically.

Previously, studies have examined specific laboratory tests in the inpatient intensive care unit setting as possible surrogate markers for adverse outcomes, including coagulation studies, markers of infection, markers of inflammation, and indicators of tissue damage [1,7–11]. A study involving 24 ICU patients due to COVID found evidence of a hypercoagulable state including elevated fibrinogen and D-dimer levels along with an associated hyper inflammatory state [12]. Another study conducted during the initial outbreak in Wuhan that examined over 1000 hospitalized patients with severe disease found significant laboratory abnormalities, namely lymphocytopenia in 83% of patients and an elevated C reactive protein in 61% of patients [1]. There were also findings of abnormally elevated D-dimer and creatine kinase, though these results were not as common as those previously mentioned [1,11]. Some groups have also explored infection markers, such as procalcitonin as a potential predictor of severe disease. A recently conducted meta-analysis of 4 studies found that there may be a nearly 5 fold increase in the risk of severe disease in the setting of elevated procalcitonin in hospitalized patients [13].

Imaging is another possible diagnostic modality that can help with the identification of COVID19. One study found chest CT imaging to have a higher sensitivity than that of the PCR test [5]. The majority of radiologic findings in severe disease cases reveal diffuse bilateral lung involvement. Ground glass opacities may be seen along with increased vascular markings and is likely due to immune mediated lung damage leading to fluid leaking into the alveoli [14]. The timeline of symptom onset and seeing abnormalities on imaging is estimated to peak around 10 days, but data is still limited [15]. It is also possible to see imaging abnormalities in asymptomatic cases according to a study of 81 patients in

Wuhan [15]. Recovery from disease can also manifest as distinct radiologic findings, which another group described as “fibrous stripes” [16]. Given such findings, chest imaging modalities such as X-ray or CT may prove to be invaluable in diagnosis. Currently, the American Journal of Radiology recommends use of chest imaging as a first line in diagnosis of suspected COVID19 infection.

While the situation is still evolving and under significant investigation, it is consistently seen in current studies that abnormal findings in both laboratory studies and imaging are more likely to correspond with severe disease. While the aforementioned studies explored laboratory findings in hospitalized patients, we believe that there may be utility in those same studies in the ED in addition to current diagnostic testing, medical interviewing, and physical examination findings when devising disposition planning for patients.

Since 2019, the house of medicine has been working diligently to better characterize the COVID19 virus and how it effects the human body. As the world has seen the negative impacts on the neighborhood of an overwhelmed hospital system, we aim to help offer a greater understanding to safe disposition planning of COVID cases. Predicting safe discharge for those identified as lower risk can help alleviate the burden of overwhelming hospitalization volume in the setting of this pandemic. Additionally, and possibly more importantly, we hope to gauge which patients are presumed to have a more severe progression of the disease whose care is best fit to be in the inpatient setting. The primary goal of this study was to identify if a combination of diagnostics measures and patient symptomology would be better than COIVD19 PCR in predicting which patients are truly infected with the COVID19 virus. The secondary goal was to identify if a combination of diagnostic measures in conjunction with a pattern of patient symptoms, would accurately predict which patients are more likely to follow a severe course of the disease in attempt to help guide disposition planning.

2. Methods:

2.1 Study design

A retrospective cohort study examined suspected cases presenting at a level one academic health center adult emergency department between March 2020 and August 2020. These cases were categorized accordingly based on COVID PCR testing that included tests conducted from both outside facilities and in the ED. The PCR positive cases that initially presented to the ED for any medical reason other than COVID19 were excluded (such as trauma, stroke, substance abuse, psychiatric, etc.), with the remaining cases being eligible for this study.

Cases were further categorized according to disposition groups: ED discharge, inpatient discharge NMC (no medical complications), and inpatient discharge MCM (medical complications or morgue). Patients were considered to have a complication if any of the following occurred during their hospitalization; pneumonia confirmed on chest imaging, endotracheal intubation or noninvasive positive pressure ventilation (NIPPV), need for vasopressors, central line placement, bronchoscopy, lung biopsy, chest tube placement or drain placement, received broad spectrum antibiotics. Patients were included in this category in cases where death resulted from any COVID19 complication. The ED discharge group included all corresponding cases discharged home or to nursing facility. The inpatient discharge NMC group included all corresponding cases discharged home or to nursing facility. The inpatient discharge MCM included all corresponding cases either discharged home or to nursing facility after resolution of hospital course complications or died following hospital course complications.

Patient data including demographics (age, gender, race, past medical history for comorbidities), symptomology (cough, sore throat, congestion, myalgias, fatigue, shortness of breath, headache, nausea, vomiting, diarrhea, abdominal pain, loss of taste or smell, chest pain), physical examination (abnormal lung or heart sounds, abnormal pulse, fever, hypertension, tachypnea, tachycardia), imaging (chest), and laboratory studies (white blood cells, sodium, potassium, calcium, bicarbonate, chloride,

creatinine, glucose, BUN, creatine kinase, D-dimer, lactic acid, ProBNP, troponin, LDH, procalcitonin, CRP, ESR, PT INR, PTT) were collected. For laboratory results obtained after patients had been admitted, the earliest results were recorded. All data was abstracted from the electronic health record (EPIC) by a single trained fourth year medical student that was aware of the study objects. Data was abstracted directly into an excel data file. This study was determined to be exempt by the institutional review board.

2.2 Data Analysis

In our analysis, we compared the three disposition groups: ED discharge, inpatient discharge NMC, and inpatient discharge MCM. All analysis was conducted in R studio. Chi-squared test with corresponding Bonferroni correction for multiple comparisons was used in the analysis of categorical variables, including demographics, symptomology, physical examination, and imaging studies with an adjusted p value of 0.0167. An ANOVA and Welch's T test were used for analysis of continuous variables, including age, and laboratory testing. Post hoc testing was conducted for the ANOVA analysis to account for multiple comparisons using the Tukey test. After training the investigator reviewed the first 10% of cases to assure accuracy and determine if additional training was required. After this analysis, further training was deemed to be unnecessary since methods had been consistent and the data extracted was relatively uncomplicated. Missing data from the electronic health records were not presumed to be negative and were subsequently not included in the analysis of the variable.

3. Results:

Of the 458 suspected cases that presented 239 cases tested PCR positive, 37 of which were excluded from further investigation due to presentation for other explainable medical reasons. Among the 219 PCR negative cases, 67 presented due to other medical reasons, 35 were asymptomatic, and 117 were symptomatic with no other explanation. Of the remaining PCR positive cases, 74 were discharged from

the ED and 128 were admitted inpatient. Among those admitted to the inpatient unit, 52 were discharged with no complications arising during their stay, 45 were discharged following complications or invasive interventions, and 31 were discharged to the morgue.

Demographic data, symptomatology, and physical exam findings are presented in Table 1. The average ages of both inpatient groups were higher than that of the ED discharge group ($p < 0.01$). The only significant differences in race between groups was in in those who identified as "White or Caucasian" and "Black or African American". There was a significantly higher percentage of those who identified as "Black or African American" in the ED discharge group compared to the inpatient discharge MCM group ($p < 0.01$). There was a significantly higher percentage of those who identify as "White or Caucasian" in the inpatient discharge MCM group compared to the ED discharge group ($p < 0.01$).

Overall, cases of severe disease had more extensive medical histories. The ED discharge group had a significantly lower percentage of having any past medical history compared to both inpatient groups ($p < 0.01$). The comparisons between groups are presented in Table A2 in the appendix. The medical conditions with significant differences between groups were hypertension ($p < 0.01$), heart disease ($p < 0.01$), diabetes ($p < 0.01$), and cancer ($p < 0.024$). There was a significantly lower percentage of heart disease and diabetes history in both noncomplicated groups (ED discharge and inpatient discharge), compared to the inpatient discharge with complications group ($p < 0.01$). Hypertension was significantly less in the ED discharge group compared to both inpatient groups ($p < 0.01$). Cancer history was less in the ED discharge group compared to the inpatient discharge with complications group ($p < 0.01$).

The most common symptoms were cough (70.63%), fatigue (77%), and shortness of breath (59%). The comparisons of symptoms between groups are also presented in Table A2. There were no significant differences between the three groups in the prevalence of cough. There were significant differences between groups for the prevalence of fatigue ($p < 0.01$) and shortness of breath ($p < 0.01$). The

percentages of shortness of breath, and fatigue were higher in the inpatient discharge MCM group compared to the ED discharge group ($p < 0.01$). Of note, most symptoms had low sample sizes ($N < 20$). With regards to small sample sizes for these variables, there were differences between groups for sputum, vomiting, and abnormal lung sounds, abdominal tenderness, and skin abnormalities. Further analysis for multiple groups was not pursued due to limited sample sizes.

Abnormal lung sounds were the most common physical exam finding (22.6% overall). The inpatient discharge MCM group had a higher proportion of abnormal physical exam findings compared to the others (table 1). However, most physical exam findings had small sample sizes ($N<10$) and further analysis for multiple groups was not pursued. There were no significant differences in the initial ED vital signs across all groups. Of the 202 cases investigated, 117 of the 168 chest scans performed (accounting for both chest x-ray and chest CT) yielded acutely abnormal results. Both inpatient groups exhibited higher percentages of abnormal chest scans than that of the ED discharge group shown in table A1 in the appendix ($p < 0.01$).

In our cohort, there were no differences between groups in terms of white blood cell count and most of the items on metabolic panels. There was a difference between groups in BUN that was both clinically and statistically significant ($p < 0.01$). The ED discharge group had a lower mean BUN compared to the inpatient discharge MCM group (14.00 mg/dL vs. 30.85 mg/dL, $p < 0.01$). The mean of the ED discharge group was within normal reference ranges, whereas the mean of the inpatient discharge group was elevated. The inpatient discharge NMC group had a lower mean BUN compared to the inpatient (19.73 mg/dL vs. 30.85 mg/dL, $p < 0.013$). Of note, both means are elevated above normal reference ranges. Analysis of inpatient laboratory testing revealed that overall, the inpatient discharge MCM group exhibited higher abnormal results for creatine kinase ($p = 0.036$), lactic acid ($p = 0.048$), troponin ($p = 0.011$), procalcitonin ($p = 0.041$), inflammatory markers (CRP and ESR, both $p < 0.01$), and coagulation studies (PT, PTT, $p = 0.041$ and $p < 0.01$, respectively). Further details of these comparisons can be found

in table 3. There was also no permutation of symptomology, physical examination findings, imaging, or laboratory testing results that was shown to be more sensitive than that of the PCR test in this study.

For all the variables, further details of comparisons between the three disposition groups can be found in the appendix (tables A1 and A2).

Table 1. Patient Comparison of Demographics and Past Medical History between Disposition Groups.

	ED (No.)	No Complications(No.)	Complications(No.)	P (overall)
Mean Age	40.49 (74)	60.13 (52)	66.75 (76)	<0.01*
Male	44.59% (33)	55.77% (29)	50% (38)	0.464
Female	55.41% (41)	44.23% (23)	50% (38)	0.464
Asian	2.70% (2)	3.85% (2)	3.95% (3)	0.903
Native American	1.35% (1)	1.96% (1)	1.32% (1)	0.955
Hispanic	4.05% (3)	3.85% (2)	6.58% (5)	0.708
Other	12.16% (9)	7.69% (4)	7.89% (6)	0.594
White or Caucasian	31.08% (23)	48.08% (25)	57.89% (44)	<0.01*
Black or African American	48.65% (36)	34.62% (18)	22.37% (17)	<0.01*
Any Past Medical History	62.5% (45)	90% (45)	92.86% (65)	<0.01*
Current Smoker	16.44% (12)	12.24% (6)	11.59% (8)	0.666
Hypertension	36.11% (26)	63.27% (31)	72.86% (51)	<0.01*
Diabetes	23.61% (17)	32.65% (16)	56.52% (39)	<0.01*
Chronic Liver Disease	5.56% (4)	4.08% (2)	4.35% (3)	0.915
Cancer	4.23% (3)	12.24% (6)	19.12% (13)	0.024*
Heart Disease	6.94% (5)	8.16% (4)	42.03% (29)	<0.01*
Lung Disease	20.83% (15)	22% (11)	22.86% (16)	0.958
Immunosuppressed	2.78% (2)	6.12% (3)	2.90% (2)	0.575

Disposition Groups: ED, Discharged from Emergency Department; No complications, All discharged from inpatient with no complications; Complications, all discharged from inpatient following

complications, invasive procedures, or to the morgue
*A p value of <0.05 was considered significant, prompting a Bonferroni correction for multiple comparisons. See table

Table 2. Comparison of Initial ED Clinical Presentation between Disposition Groups

	ED% (No.)	No Complications% (No.)	Complications% (No.)	P (Overall)
Cough	64.29% (45)	73.81% (31)	77.08% (37)	0.283
Sore Throat	13.33% (4)	15.79% (3)	14.81% (4)	0.383
Congestion	16.67% (7)	38.89% (7)	31.03% (9)	0.146
Myalgias	56.67% (17)	70.59% (12)	58.82% (10)	0.629
Fatigue	50.00% (17)	70.59% (12)	87.50% (28)	<0.01*
SOB	42.65% (29)	63.64% (28)	77.36% (41)	<0.01*
Headache	29.82% (17)	39.13% (9)	19.35% (6)	0.276
Nausea	15.15% (10)	30.56% (11)	26.19% (11)	0.154
Vomiting	4.35% (3)	17.14% (6)	25.00% (11)	<0.01*
Diarrhea	19.40% (13)	20.00% (7)	22.50% (9)	0.926
Abdominal Pain	8.70% (6)	17.95% (7)	11.63% (5)	0.361
Loss Taste/Smell	85.71% (6)	100.00% (1)	83.33% (5)	0.907
Chest Pain	25.37% (17)	31.58% (12)	14.89% (7)	0.180
Abnormal Lung sounds	0.76% (5)	15.69% (8)	43.24% (32)	<0.01*
Abnormal Heart Sounds	2.70% (2)	1.92% (1)	1.35% (1)	0.852
Pulse (Abnormal)	29.41% (5)	27.27% (3)	47.62% (10)	0.389
Fever (>38.5C)	2.70% (2)	7.69% (4)	6.76% (5)	0.403
Hypertension	41.10% (30)	57.69% (30)	37.84% (28)	0.069
Tachypnea	67.57% (50)	76.92% (40)	82.43% (61)	0.106
Tachycardia	20.55% (15)	21.15% (11)	31.08% (23)	0.265
Abnormal Chest Imaging	42.86% (18)	76.92% (40)	78.67% (59)	<0.01*

Disposition Groups: ED, Discharged from Emergency Department; No complications, All discharged from inpatient with no complications; Complications, all discharged from inpatient following complications, invasive procedures, or to the morgue

*A p value of <0.05 was considered significant, prompting a Bonferroni correction for multiple comparisons. See table

Table 3. Comparison of Laboratory Studies according to Disposition and Hospitalization Outcome

Test (Reference ranges)	ED (Mean, N)	No Complications (Mean, N)	Complications (Mean, N)	P (Overall)
White Blood Count (4500-11,000/mm^3)	6.52 (43)	6.49 (52)	7.91 (74)	0.084
Sodium (136-145 mEq/L)	137.25 (48)	137.27 (52)	137.27 (74)	0.990
Potassium (3.5-5.0 mEq/L)	3.96 (48)	4.10 (52)	4.2 (74)	0.061
Calcium, serum (8.4-10.2 mg/dL)	9.03 (42)	9.39 (49)	10.06 (72)	0.792
Bicarbonate (22-28 mEq/L)	23.06 (48)	23.48 (52)	22.69 (74)	0.632
Chloride (95-105 mEq/L)	101.38 (48)	99.71 (52)	97.57 (74)	0.276
Creatinine (0.6-1.2 mg/dL)	1.33 (48)	1.24 (52)	1.70 (74)	0.351
Glucose (70-140 mg/dL)	117.81 (48)	128.60 (52)	172.15 (74)	<0.01*
BUN (7-18 mg/dL)	14 (48)	19.73 (52)	30.58 (74)	<0.01*
Creatine Kinase (<90 U/L)	-**	123.41 (22)	266.66 (44)	0.036*
D Dimer (<0.50 ug/mL)	-**	2.02 (40)	2.80 (65)	0.172
Lactic Acid (0.5 – 2.2 mmol/L)	-**	1.34 (34)	1.77 (67)	0.048*
ProBNP (<450pg/mL)	-**	1348.53 (32)	2824.08 (52)	0.142
Troponin (<0.01ng/mL)	-**	0.01 (40)	0.05 (67)	0.011*
LDH (122 – 225 U/L)	-**	359.97 (33)	415.83 (52)	0.066
Procalcitonin (<0.1ng/mL)	-**	0.13 (33)	18.89 (63)	0.041*
CRP (<8.0mg/L)	-**	46.56 (40)	116.50 (62)	<0.01*
ESR (<20mm/hr)	-**	44.59 (37)	63.39 (59)	<0.01*
PT (12.5s -14.9s)	-**	15.60 (23)	18.89 (50)	0.041*
INR (Clinically individualized)	-**	1.25 (23)	1.61 (50)	0.045
PTT (24.0s -33.0s)	-**	29.36 (10)	36.93 (20)	<0.01*

Disposition Groups: ED, Discharged from Emergency Department; No complications, All discharged from inpatient with no complications; Complications, all discharged from inpatient following

complications, invasive procedures, or to the morgue
Abbreviations: BUN, Blood Urea Nitrogen; ProBNP, B-type natriuretic peptide; LDH, Lactate Dehydrogenase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PT, Prothrombin Time; INR, International Normalized Ratio; PTT, Partial Thromboplastin Time
INR: No reference value included since it is clinically individualized depending on relevant medications
*A p value of <0.5 was considered statistically significant. Variables with multiple comparisons were subject to post-hoc testing (see table 4).
**Corresponding results were recorded for the ED discharge group, but were not included in the final analysis due to low sample size (N < 10)

4. Discussion

One of major challenges with diagnosing and triaging patients who present to the ED with suspected COVID19 is the wide range of presentations. Our goals with this retrospective study were two-fold. First, we wanted to assess the possibility of supplementing current diagnosis testing under the premise that data regarding the sensitivity of the PCR test is limited. One previous study had found that the PCR test had a sensitivity of 70%, and in the initial investigation of our cohort, we found a similar percentage of 66.1%. By obtaining data regarding symptomology, physical examination, imaging, and laboratory testing, we wanted to determine if there were possible surrogate markers of COVID19 that would prove to be more sensitive than the PCR test. We performed calculations using the most common findings in each modality, treating them as mutually exclusive presentations, and found that there was no permutation of findings that was more sensitive than that of the current PCR test. Our second goal was using this data to possibly determine the triage and use in disposition planning of patients who initially present to the ED.

In accordance with other studies, we found that the most common symptoms in our cohort were cough (70.63%), fatigue (77%), and shortness of breath (59%) [1,8,11]. GI symptoms were not as common, with

nausea, vomiting, and diarrhea occurring at 22%, 13.5%, and 20.4% respectively. Similarly, cases of severe disease corresponded with a higher frequency of abnormal radiologic findings.

Upon our analysis of laboratory data, we did not find lymphocytopenia as a prominent finding, unlike what was observed previously by a group in China [1]. However, we did find that more severe cases presented with extensive laboratory abnormalities at significantly higher values compare to that of less severe cases. Specifically, we saw abnormalities in inflammatory markers (CRP and ESR), coagulation studies (D-dimer, PT, PTT, INR), infection markers (procalcitonin), and markers of tissue damage (troponin, creatine kinase, and lactic acid). These findings may likely be secondary to COVID19 as severe disease may be associated with exacerbation of pre-existing conditions, acute decompensation, or superimposed infections. It should also be noted that most of these aforementioned laboratory studies were above normal limits in cases that were admitted inpatient. Nonetheless, more extensive abnormalities seem to correlate with disease severity.

Given that COVID19 is a novel disease, the exact pathogenesis is not well understood. Our data may shed light on current speculations and existing studies. First, we found neither lymphocytopenia nor lymphocytosis in most cases across all groups. In fact, most recorded values were within normal ranges. This finding may be attributed to the timing of data collection since almost all the recorded results were obtained in the ED, whereas previous studies were conducted in the inpatient setting. Since lymphocytes play a major role in the immunologic response against infections, it is possible that our results may be in accordance with previous studies if we had followed complete blood count results throughout the entire hospital course. The pathogenesis of lymphocytopenia is speculated to be two-fold. First, by hindering production, and second, by inducing apoptosis. Both potential mechanisms may occur through the ACE2 receptors [17]. Coronaviruses interact with such receptors to enter host cells. These receptors are found in lymphocytes, which the virus may enter and induce apoptosis [9].

Additionally, these receptors are also found within the thymus, which plays a crucial role in the production of lymphocytes [18].

There has also been significant interest in the possible coagulation abnormalities seen with COVID19, which our findings support. This observation may also be explained by the interaction between coronaviruses and the ACE2 receptor. This receptor is found in endothelial cells that line blood vessels. Interaction with SARS-CoV2 can lead to activation of coagulation cascades, leading to the respective coagulation abnormalities seen in severe cases of COVID19 [19].

Our most significant finding was seen in inflammatory markers. Nearly all cases admitted inpatient revealed CRP and ESR above normal reference ranges. However, these values were significantly higher in cases of severe disease. The mean CRP and ESR seen in the complicated inpatient group were 116.5 and 63.39, respectively. Other studies have found similar findings. Among these findings, a recent meta-analysis has referenced "high" values for inflammatory markers in severe disease [9]. However, it is still difficult to recommend clinical "cutoffs" with current data.

While we found significant differences between groups for glucose and INR, these differences are likely not clinically relevant. First, the glucose tests were conducted in the ED as part of a basic metabolic panel and results can vary depending on multitude of factors, including medication history, past medical history, or fasting state. INR values can also vary widely depending and is clinically individualized based on past medical history and medications taken.

There were several limitations in our study. First, the length of this study was conducted over the course of 5 months, primarily during the spring and summer. Second, there were issues regarding small sample sizes. This is largely related to how the data was collected. When this project was first conceived, we had devised a robust list of variables to investigate. For each case, we examined the first documented ED encounter note. If a variable of interest was not documented, it was not counted in our analysis. A large

portion of categorical variables were not documented in the initial encounter. Given the work conditions in the ED, it often is not practical for clinicians to obtain information of every possible symptom or physical exam finding, which may have accounted for the low sample size for some variables.

Although many cases were excluded from further investigation due to clear presentation due to other medical explanations, it is difficult to discern if the remaining COVID19 positives cases truly presented solely due to COVID19. This limitation was particularly relevant to cases with an extensive list of comorbidities. Given the limitations with sample size, for some groups occurring as low as single digits, we opted not to perform the corresponding analysis. This occurred primarily with laboratory testing, the majority of which were conducted in the inpatient setting only. Furthermore, there was no established criteria regarding how long since the initial ED encounter laboratory studies would still be counted. Some results were obtained simultaneously at admission, while others were obtained days after admission. There were also several cases among our cohort that initially presented to the ED and were discharged home, only to return days later to be admitted inpatient. While we did not investigate these cases in further detail, the initial ED documentation did not reveal significant findings which did not result in follow up with laboratory testing.

Despite these limitations, we believe that our findings hold promise in assisting clinicians in the ED setting. Given the wide range of disease presentation, performing laboratory tests, namely inflammatory markers, infection markers, coagulation studies, and possibly markers of tissue damage may prove to be invaluable in triaging or formulating disposition planning for patients, especially those who present atypically or are medically complex.

5. Conclusion

COVID19 can vary widely in presentation and disease severity can progress rapidly. Abnormal findings on radiologic imaging and laboratory testing are correlated with severe disease. These tests include

inflammatory markers (CRP, ESR), coagulation studies (PTT, INR, PT, D-dimer), and markers of tissue damage (troponin, creatine kinase, lactic acid), and markers of infection (procalcitonin). Our findings suggest that in severe cases, these aforementioned tests are elevated significantly above normal ranges.

As we have since learned from the growing research across the globe, inflammatory changes in the setting of active COVID19 infections seems to be one of the most common denominators in the disease. The tests as noted above, in many ways are direct or surrogate markers of inflammatory changes from the body's baseline and can help quantitatively measure the overt inflammatory changes that take place in the body of an infected individual which seem to be correlated to disease progression and severity. Given such findings, there may be utility in the implementation of these tests in the ED setting as a supplement to current PCR testing. The time period of this study was selected as a response to the initial outbreak during the spring and early summer months in the United States since guidelines regarding the triage were limited. This study period was not selected to present a specific time of year, but rather to bridge the gap in using limited data under dynamic circumstances to correlating clinically in an emergency setting. The rationale in performing such tests and interpretation of our results should be correlated clinically, but may prove to be invaluable in the triage and disposition planning of patients who initially present to the ED.

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Appendix

Table A1. Expanded Comparisons of Disposition Groups for Demographics, PMH, and Clinical Presentation		
		P
Black or African American	ED (48.65%) vs No Complications (48.65%)	0.117
	ED (48.65%) vs Complications (22.37%)	<0.01**
	No Complications (48.65%) vs Complications (22.37%)	0.127
White or Caucasian	ED (31.08%) vs No Complications (48.08%)	0.053
	ED (31.08%) vs Complications (57.89%)	<0.01**
	No Complications (48.08%) vs Complications (57.89%)	0.273
Any Past Medical History	ED (62.5%) vs No Complications (90%)	<0.01**
	ED (62.5%) vs Complications (92.86%)	<0.01**
	No Complications (90%) vs Complications (92.86%)	0.557
Hypertension	ED (36.11%) vs No Complications (63.27%)	<0.01**
	ED (36.11%) vs Complications (72.86%)	<0.01**
	No Complications (63.27%) vs Complications (72.86%)	0.266
Diabetes	ED (23.61%) vs No Complications (32.65%)	0.273
	ED (23.61%) vs Complications (56.52%)	<0.01**
	No Complications (32.65%) vs Complications (56.52%)	<0.01**
Cancer	ED (4.23%) vs No Complications (12.24%)	0.101
	ED (4.23%) vs Complications (19.12%)	<0.01**
	No Complications (12.24%) vs Complications (19.12%)	0.32
Heart Disease	ED (6.94%) vs No Complications (8.16%)	0.802
	ED (6.94%) vs Complications (42.03%)	<0.01**
	No Complications (8.16%) vs Complications (42.03%)	<0.01**
Shortness of Breath	ED (42.65%) vs No Complications (63.64%)	0.03

	ED (42.65%) vs Complications (77.36%)	<0.01**
	No Complications vs Complications (63.64%)	0.138
Fatigue	ED (50.00%) vs No Complications (70.59%)	0.162
	ED (50.00%) vs Complications (87.50%)	<0.01**
	No Complications (70.59%) vs Complications (87.50%)	0.146
Abnormal Lung Sounds	ED (6.76%) vs No Complications (15.69%)	0.108
	ED (6.76%) vs Complications (43.24%)	<0.01**
	No Complications (15.69%) vs Complications (43.24%)	<0.01**
Abnormal Chest Imaging	ED (42.86%) vs No Complications (76.92%)	<0.01**
	ED (42.86%) vs Complications (78.67%)	<0.01**
	No Complications (76.92%) vs Complications (78.67%)	0.787
**A p value of <0.0167 was significant. This was calculated following a Bonferroni correction for three separate comparisons		
Abbreviations: PMH, Past Medical History		

Table A2. Tukey Test for Multiple Comparisons For Mean Age and Laboratory Testing

		P Value
Mean Age	ED (40.49) vs No Complications (60.13)	<0.01*
	ED (40.49) vs Complications (66.75)	<0.01*
	No Complications (60.13) vs Complications (66.75)	0.067
Glucose	ED (117.81) vs No Complications (128.60)	0.815
	ED (117.81) vs Complications (172.15)	<0.01*
	No Complications (128.60) vs Complications (172.15)	0.019
BUN	ED (14) vs No Complications (19.73)	0.359
	ED (14) vs Complications (30.58)	<0.01*

	No Complications (19.73) vs Complications (30.58)	0.013*
*A p value of <0.05 was considered significant		

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Danny Zheng, MD: Conceptualization, Data Curation, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing **David Andonian, MD**: Conceptualization, Methodology, Supervision, Writing – Review & Editing **Susan Wojcik, PhD**: Project Administration, Formal Analysis, Writing – Original Draft, Writing – Review & Editing